Amendments To The Claims

1. (Canceled)

2. (Amended herein) The method of Claim 33 wherein R^3 is:

(a) optionally substituted heterocyclyl;

(b) aryl or heteroaryl both optionally substituted with a substituent selected from halo, alkyl, amino, alkoxy, carboxy, lower alkoxy carbonyl, SO_2R' (where R' is alkyl) or $SO_2NR'R''$ (where R' and R" are independently hydrogen or alkyl);

(c) heteroalkyl;

(d) heteroalkenyl;

(e) heteroalkoxy;

(f) optionally substituted heterocyclylalkyl or heterocyclyloxy;

(g) optionally substituted heterocyclylalkenyl;

(h) optionally substituted heterocyclylalkynyl;

(i) optionally substituted heterocyclylalkoxy;

(j) optionally substituted heterocyclylalkylamino;

(k) optionally substituted heterocyclylalkylcarbonyl;

(l) -Y-(alkylene)-R^9 where Y is a single bond, -O- or -NH- and R^9 is optionally substituted heteroaryl, $-CONR^{12}R^{13}$, $-SO_2R^{14}$, $-SO_2NR^{15}R^{16}$, $-NHSO_2R^{17}$ or $-NHSO_2NR^{18}R^{19}$ where R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18} and R^{19} are independently of each other hydrogen, alkyl or heteroalkyl;

(m) cycloalkylalkyl, cycloalkylalkynyl and cycloalkylalkynyl, all optionally substituted with alkyl, halo, hydroxy or amino;

(n) arylaminoalkylene or heteroarylaminoalkylene; or

(o) Z-alkylene-$NR^{30}R^{31}$ where Z is -NH-, -N(alkyl)- or -O-, and R^{30} and R^{31} are independently of each other, hydrogen, alkyl or heteroalkyl~~, wherein~~

~~said alkylene and alkyl groups are optionally substituted with one to two groups selected from OH and O(alkyl)~~.

3. (Original) The method of Claim 2 wherein R^1 and R^2 are hydrogen; and B is phenyl.

4. (Original) The method of Claim 3 wherein A is phenyl.

5. (Original) The method of Claim 4 wherein R^4 is hydrogen; and R^5 is halo or alkyl.

6. (Original) The method of Claim 5 wherein R^5 is chloro, fluoro or methyl; and R^6 is hydrogen, chloro, fluoro, methyl or methoxy.

7. (Original) The method of Claim 5, wherein R^3 is optionally substituted heteroaryl.

8. (Original) The method of Claim 7, wherein R^3 is pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, N-oxidopyridin-2-yl, N-oxidopyridin-3-yl, N-oxidopyridin-4-yl or pyridon-2-yl, all optionally substituted.

9. (Original) The method of Claim 8, wherein R^3 is at the 3-position.

10. (Original) The method of Claim 9, wherein R^5 is 4-F and R^6 is hydrogen.

11. (Original) The method of Claim 9, wherein R^5 is 2-Me and R^6 is hydrogen.

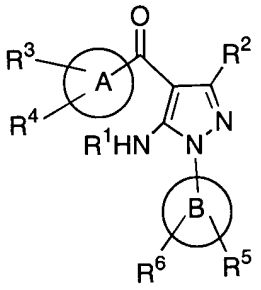
12. (Original) The method of Claim 5, wherein R^3 is optionally substituted phenyl.

13. (Original) The method of Claim 12, wherein R^3 is 3-sulfamoylphenyl, 3-methylsulfonylphenyl, 3-carboxyphenyl or 3-ethoxycarbonylphenyl.

14. (Original) The method of Claim 13, wherein R^3 is at the 3-position.

15. (Original) The method of Claim 14, wherein R^5 is 4-F and R^6 is hydrogen.

16. (Amended Herein) ~~**The method of Claim 5 wherein R^3 is:**~~ **A method of treatment of a disease in a mammal treatable by administration of a p38 MAP kinase inhibitor, comprising administration to the mammal a therapeutically effective amount of a compound of Formula (I):**



(I)

wherein:

R^1 is hydrogen or acyl;

R^2 is hydrogen or alkyl;

A is an aryl ring;

B is an aryl ring;

R^3 is:

~~(a) heteroalkyl~~;

(**~~b~~a**) heteroalkoxy;

(**~~c~~b**) optionally substituted heterocyclylalkyl;

(**~~d~~c**) optionally substituted heterocyclylalkoxy;

(**ed**) optionally substituted heterocyclylalkylamino;

(~~f~~e) -Y-(alkylene)-R^9 where Y is a single bond, -O- or -NH- and R^9 is optionally substituted heteroaryl, -$CONR^{12}R^{13}$, SO_2R^{14}, -$SO_2NR^{15}R^{16}$, -$NHSO_2R^{17}$ or -$NHSO_2NR^{18}R^{19}$ where R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18} and R^{19} are independently of each other hydrogen, alkyl or heteroalkyl; ~~or~~

(f) heteroaryl selected from pyridinyl, N-oxidopyridinyl or pyridonyl; or

(g) substituted phenyl selected from sulfamoylphenyl, methylsulfonylphenyl, carboxyphenyl or ethoxycarbonylphenyl;

R^4 is:

(a) hydrogen;

(b) halo;

(c) alkyl;

(d) alkoxy; and

(e) hydroxy;

R^5 is:

(a) hydrogen;

(b) halo;

(c) alkyl;

(d) haloalkyl;

(e) thioalkyl;

(f) hydroxy;

(g) amino;

(h) alkylamino;

(i) dialkylamino;

(j) heteroalkyl;

(k) optionally substituted heterocycle;

(l) optionally substituted heterocyclylalkyl;

(m) optionally substituted heterocyclylalkoxy;

(n) alkylsulfonyl;

(o) aminosulfonyl, mono-alkylaminosulfonyl or dialkylaminosulfonyl;

(p) heteroalkoxy; and

(q) carboxy;

R^6 is:

(a) hydrogen;

(b) halo;

(c) alkyl; and

(d) alkoxy;

or a prodrug, individual isomer, mixtures of isomers, pharmaceutically acceptable salt or solvate thereof.

22. (Original) The method of Claim 16, wherein R^3 is heteroalkoxy.

23. (Original) The method of Claim 22, wherein R^3 is at the 3-position and is selected from the group consisting of 3-dimethylaminopropoxy, 2-dimethylaminoethoxy, 2-hydroxyethoxy, 2,3-dihydroxypropoxy, and 2,2-(dihydroxymethyl)ethoxy.

24. (Original) The method of Claim 23 wherein R^5 is 4-F or 2-Me and R^6 is hydrogen.

25. (Original) The method of Claim 16, wherein R^3 is optionally substituted heterocyclylalkyl, optionally substituted heterocyclylalkoxy or optionally substituted heterocyclylalkylamino.

26. (Original) The method of Claim 25, wherein R^3 is at the 3-position and is selected from the group consisting of 3-(morpholin-4-yl)propoxy, 2-(morpholin-4-yl)ethoxy, 2-(2-oxo-pyrrolidin-1-yl)ethoxy, 3-(morpholin-4-yl)propyl, 2-(morpholin-4-yl)ethyl, 4-(morpholin-4-yl)butyl, 3-(morpholin-4-yl)propylamino, 2-(morpholin-4-yl)ethylamino, 4-hydroxy-

piperidinylmethyl, 2-(S,S-dioxo-thiamorpholin-4-yl)ethyl, 3-(S,S-dioxo-thiamorpholin-4-yl)propyl and N-methylpiperazinylmethyl.

27. (Original) The method of Claim 26 wherein R^5 is 4-F or 2-Me and R^6 is hydrogen.

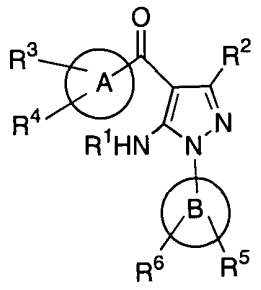
28. (Original) The method of Claim 16 wherein R^3 is -Y-(alkylene)-R^9 where Y is a single bond, -O- or -NH- and R^9 is optionally substituted heteroaryl, -$CONR^{12}R^{13}$, -SO_2R^{14}, -$SO_2NR^{15}R^{16}$, -$NHSO_2R^{17}$ or -$NHSO_2NR^{18}R^{19}$ where R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18} and R^{19} are independently of each other hydrogen, alkyl or heteroalkyl.

29. (Original) The method of Claim 28, wherein Y is a single bond and R^9 is -SO_2R^{14} or -$SO_2NR^{15}R^{16}$.

30. (Original) The method of Claim 29 wherein R^3 is methylsulfonylethyl or sulfamoylethyl.

31. (Original) The method of Claim 30 wherein R^5 is 4-F or 2-Me and R^6 is hydrogen.

33. (Amended herein) A method of treatment of a disease in a mammal treatable by administration of a p38 MAP kinase inhibitor, comprising administration to the mammal a therapeutically effective amount of a compound selected from the group of compounds represented by Formula (I):



(I)

wherein:

R^1 is hydrogen or acyl;

R^2 is hydrogen or alkyl;

A is an aryl ring;

B is an aryl ring;

R^3 is selected from the group consisting of:

(a) acylamino;

(b) optionally substituted heterocyclyl;

(c) optionally substituted aryl or heteroaryl;

(d) heteroalkenyl;

(e) heteroalkynyl;

(f) heteroalkoxy;

(g) optionally substituted heterocyclylalkyl;

(h) optionally substituted heterocyclylalkenyl;

(i) optionally substituted heterocyclylalkynyl;

(j) optionally substituted heterocyclylalkoxy, cyclyloxy, or heterocyclyloxy;

(k) optionally substituted heterocyclylalkylamino;

(l) optionally substituted heterocyclylalkylcarbonyl;

(m) $-NHSO_2R^6$ where R^6 is optionally substituted heterocyclylalkyl;

(n) $-NHSO_2NR^7R^8$ where R^7 and R^8 are, independently of each other, hydrogen, alkyl or heteroalkyl;

(o) -Y-(alkylene)-R^9 where:

Y is a single bond, -O-, -NH- or $-S(O)_n-$ (where n is an integer from 0 to 2); and R^9 is cyano, optionally substituted heteroaryl, -COOH, $-COR^{10}$, $-COOR^{11}$, $-CONR^{12}R^{13}$, $-SO_2R^{14}$, $-SO_2NR^{15}R^{16}$, $-NHSO_2R^{17}$ or $-NHSO_2NR^{18}R^{19}$, where R^{10} is optionally substituted heterocycle, R^{11} is alkyl, and R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18} and

R^{19} are, independently of each other, hydrogen, alkyl or heteroalkyl;

(p) $-C(=NR^{20})(NR^{21}R^{22})$ where R^{20}, R^{21} and R^{22} independently represent hydrogen, alkyl or hydroxy, or R^{20} and R^{21} together are $-(CH_2)_n-$ where n is 2 or 3 and R^{22} is hydrogen or alkyl;

(q) $-NHC(=X)NR^{23}R^{24}$ where X is O or S, and R^{23} and R^{24} are, independently of each other, hydrogen, alkyl or heteroalkyl;

(r) $-CONR^{25}R^{26}$ where R^{25} and R^{26} independently represent hydrogen, alkyl, heteroalkyl or optionally substituted heterocyclylalkyl, or R^{25} and R^{26} together with the nitrogen to which they are attached form an optionally substituted heterocyclyl ring;

(s) $-S(O)_nR^{27}$ where n is an integer from 0 to 2, and R^{27} is optionally substituted heterocyclylalkyl;

(t) cycloalkylalkyl, cycloalkylalkynyl and cycloalkylalkynyl, all optionally substituted with alkyl, halo, hydroxy or amino;

(u) arylaminoalkylene or heteroarylaminoalkylene;

(v) Z-alkylene-$NR^{30}R^{31}$ or Z-alkylene-OR^{32} where Z is -O-, and R^{30}, R^{31} and R^{32} are independently of each other, hydrogen, alkyl or heteroalkyl~~, wherein said alkylene and alkyl groups are optionally substituted with one to two groups selected from OH and O(alkyl)~~;

(w) -OC(O)-alkylene-CO_2H, <u>or</u> -OC(O)-NR'R" ~~, or CO_2NHR'~~ (where R' and R" are independently hydrogen or alkyl); and

(x) heteroarylalkenylene or heteroarylalkynylene;

R^4 is selected from the group consisting of:

(a) hydrogen;

(b) halo;

(c) alkyl;

(d) alkoxy; and

(e) hydroxy;

R^5 is selected from the group consisting of:

(a) hydrogen;

(b) halo;

(c) alkyl;

(d) haloalkyl;

(e) thioalkyl;

(f) hydroxy;

(g) amino;

(h) alkylamino;

(i) dialkylamino;

(j) heteroalkyl;

(k) optionally substituted heterocycle;

(l) optionally substituted heterocyclylalkyl;

(m) optionally substituted heterocyclylalkoxy;

(n) alkylsulfonyl;

(o) aminosulfonyl, mono-alkylaminosulfonyl or dialkylaminosulfonyl;

(p) heteroalkoxy; and

(q) carboxy;

R^6 is selected from a group consisting of:

(a) hydrogen;

(b) halo;

(c) alkyl; and

(d) alkoxy; and

prodrugs, individual isomers, mixtures of isomers and pharmaceutically acceptable salts thereof.

34-37 (Canceled)

38. (Previously Presented). The method of Claim 33 wherein the disease is rheumatoid arthritis.

39. (Previously Presented). The method of Claim 33 wherein the disease is adult respiratory distress syndrome.

40. (Previously Presented). The method of Claim 33 wherein the disease is asthma.

41. (Canceled)

42. (New) The method of claim 16, wherein R^3 is optionally substituted heteroaryl selected from pyridinyl, N-oxidopyridinyl or pyridonyl.

43. (New) The method of claim 42, wherein R^3 is pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, N-oxidopyridin-2-yl, N-oxidopyridin-3-yl, N-oxidopyridin-4-yl or pyridon-2-yl, each of which may be optionally substituted

44. (New) The compound of claim 28, wherein Y is -O-alkylene and R^9 is -COOH:

45. (New) The compound of claim 28, wherein R^3 is -(alkylene)-$SO_2NR^{34}R^{35}$ where R^{34} and R^{35} each independently is hydrogen or alkyl.

REMARKS

1. *Status of the Claims*

Claims 2-31, 33, 38-40 and 42-45 are pending.

Claims 2, 16, and 33 are amended herein.

Claims 42-45 are new claims.

No new matter is introduced.

Reconsideration is respectfully requested.

2. *Claim Objections*

The Examiner noted that previously entered claims 36-39 was not numbered in accordance with 37 CFR 1.126, and the Examiner re-numbered this claims as claims 38-41 respectively. The Applicants apologize for this error and thank the Examiner for making the appropriate correction.

3. *Rejections Under 35 USC 112, First Paragraph*

The Examiner rejected claims 1-16, 19-32 and 38 as failing to comply with the written description requirement in that the claims contained subject matter not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the Application was filed, had possession of the invention.

The Examiner in particular pointed out the subject matter added by Applicants' amendment of January 11, 2003, to the definitions (o) of R^3 in claim 2, the definitions (v) and (w) of R^3 in claim 33, and the definition (v) of R^3 in claim 41. The Applicants have amended claims 2 and 33 to remove the language noted by the Examiner that was added by Applicants' last Amendment. Claim 41 has been canceled. Accordingly, Applicants believe that claims 2-31, 33, 38-40 and 42-45 as presently amended meet the requirements of 35 USC §112 first paragraph.

4. *Double Patenting*

The Applicants will file a terminal disclaimer when all outstanding issues are resolved, as indicated in Applicants' previous Amendment.

5. *Rejections Under 35 USC §103*

The Examiner rejected claims 2-7, 12, 16, 22-24, 33-35 and 38-41 under 35 USC §103(a) as being unpatentable over Faraci et al., WO 94/13643 (US 5712303). The Examiner re-iterated previous bases for rejection, stating, *inter alia*, that the difference between the teachings of Faraci et al. and Applicants' invention was that of generic description of the products being administered for the intended use.

The Applicants respectfully traverse the rejection of claims 2-7, 12, 16, 22-24, 33-35 and 38-41 over Faraci et al. In order to rely on a reference as a basis for rejection of an applicants' invention, the reference must either be in the field of Applicants' endeavor or, if, not, then be reasonably pertinent to the particular problem with which the invention was concerned. *In re Oetiker*, 23 USPQ2d 1058, 1060-61 (Fed. Cir. 1992). A reference from a different field may be reasonably pertinent if it is one that logically would have commended itself to an inventor's attention in considering the problem solved by the invention. *Wang Laboratories Inc. v.Toshiba Corp.*, 26 USPQ2d 1767 (Fed. Cir. 1993).

Faraci et al. discloses corticotropin release factor (CRF) antagonists, which are well known to be usable for treatment of stress related anxiety, depression, and other CNS disorders. Applicants' invention is directed to compounds that inhibit p38 MAP kinase for treatment of autoimmune conditions such as rheumatoid arthritis, bone resorption diseases and osteoarthritis, respiratory diseases and inflammatory conditions (see, e.g., p. 35 lines 1-10 of Applicants' specification). Faraci et al., makes a generalized assertion about CRF antagonists being usbale for treatment of inflammatory disorders, upon which the Examiner has apparently focused. At the same time, the Examiner is overlooking the autoimmune and respiratory aspects of the diseases treatable by p38 MAP kinase inhibitors. The physiological bases for inflammatory

conditions are both numerous and complex. p38 MAP kinase plays an important role in the translational control of tumor necrosis factor (TNF) and Interleukin (IL)-1, and p38 MAP kinase inhibitors are recognized as being usable for treatment of diseases mediated by TNF-1 and IL-1 (p. 1-2 of Applicants' specification). Whatever anti-inflammatory capabilities may be exhibited by CRF antagonists, the Applicants respectfully point out that CRF antagonists have never been shown to modulate TNF or IL-1, or to otherwise be effective in the treatment of p38 MAP kinase inhibitor-mediated diseases such as arthritis, osteoarthritis rheumatism or respiratory conditions. Skilled persons, when designing p38 MAP kinase inhibitors, thus do not look to teachings related to drugs for different, unrelated targets such as CRF.

A *prima facie* case of obviousness requires, *inter* alia, some suggestion or motivation in the prior art to modify a reference, and a reasonable expectation of success from making such a modification. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991). Ligands that behave as antagonists for CRF could not reasonably be expected to have affinity for an unrelated target such as a kinase inhibitor, and persons skilled in the art would not be motivated to modify the chemical structure of a CRF antagonist in order to discover p38 kinase inhibitors. Further, since a CRF antagonist would not reasonably be expected to inhibit p38 MAP kinase, there could be no reasonable expectation of success in obtaining p38 MAP kinase inhibitors from modifying the CRF antagonists of Faraci et al.

Even if a finding of *prima facie* obviousness was proper in the instant case, the Applicants would request withdrawal of the rejection under 35 USC §103(a) in view of the results disclosed by Applicants specification that are entirely unexpected from the teachings of Faraci et al. Example 27 of Applicants' specification discloses that the compounds of Applicants' invention are effective at inhibition of p38 MAP kinase. This sort of activity would be unexpected from compounds obtained by modification of CRF antagonists such as those taught by Faraci et al. Further, Examples 28 and 29 illustrate the *in vitro* and *in vivo* inhibition of TNF alpha production by the compounds of Applicants' invention. Compounds designed by modification of CRF antagonists such as those of Faraci et al. could not reasonably be expected

to inhibit TNF-α production as is achieved by the compounds of Applicants' invention. Still further, Example 30 shows that Applicants' compounds are effective in an *in vivo* arthritis assay. Once again, the modification of CRF antagonists such as those of Faraci et al. could not be expected to provide such activity.

Accordingly, the Applicants submit that the Examiner's rejection of claims 2-7, 12, 16, 22-24, 33-35 and 38-41 under 35 USC §103 as unpatentable over Faraci is not proper, and Applicants respectfully requests that this rejection be withdrawn.

a. Amendments to Claim 16.

The Applicants note that, in the Office Action mailed on May 21, 2002 in the instant case, the Examiner indicated that claims 8-11, 13-15 and 25-31 were objected to as depending from a rejected base claim but would otherwise be allowable. The Applicants have amended claim 16 to make it independent in form, and to recite subject matter, by limitation of the group R^3, that the Examiner has previously indicated as being allowable. In particular, claim 16 as amended recites that R^3 may be selected from:

(a) heteroalkoxy;

(b) optionally substituted heterocyclylalkyl;

(c) optionally substituted heterocyclylalkoxy;

(d) optionally substituted heterocyclylalkylamino;

(e) -Y-(alkylene)-R^9 where Y is a single bond, -O- or -NH- and R^9 is optionally substituted heteroaryl, -$CONR^{12}R^{13}$, SO_2R^{14}, -$SO_2NR^{15}R^{16}$, -$NHSO_2R^{17}$ or -$NHSO_2NR^{18}R^{19}$ where R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18} and R^{19} are independently of each other hydrogen, alkyl or heteroalkyl;

(f) heteroaryl selected from pyridinyl, N-oxidopyridinyl or pyridonyl; or

(g) aryl selected from sulfamoylphenyl, methylsulfonylphenyl, carboxyphenyl or ethoxycarbonylphenyl.

With regard to R^3 is heteroalkoxy, the Applicants note that compound claims reciting this limitation were deemed allowable over Faraci et al. by the Examiner in the related Application Ser. No. 09/305,737, now issued as U.S. 6376527. The claims of the present case represent the corresponding method claims, and are believed allowable for the same reasons as the corresponding compound claims of Application Ser. No. 09/305,737.

The limitations in claim 16 of R^3 being optionally substituted heterocyclylalkyl, optionally substituted heterocyclylalkoxy and optionally substituted heterocyclylalkylamino. These limitations are also recited in dependent claim 25, which the Examiner indicated as being objected to but otherwise allowable if re-presented in independent form.

The limitation in claim 16 of R^3 being -Y-(alkylene)-R^9 where Y is a single bond, -O- or -NH- and R^9 is optionally substituted heteroaryl, -$CONR^{12}R^{13}$, SO_2R^{14}, -$SO_2NR^{15}R^{16}$, -$NHSO_2R^{17}$ or -$NHSO_2NR^{18}R^{19}$ where R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18} and R^{19} are independently of each other hydrogen, alkyl or heteroalkyl appears in dependent claim 28, which the Examiner previously objected to but indicated as being otherwise allowable.

The limitation of R^3 being heteroaryl selected from pyridinyl, N-oxidopyridinyl or pyridonyl is derived from previously objected to claim 8 which the Examiner indicated would also be allowable if presented in independent form.

Finally, the limitation of R^3 being substituted phenyl selected from sulfamoylphenyl, methylsulfonylphenyl, carboxyphenyl or ethoxycarbonylphenyl is obtained from claim 13, which the Examiner indicated would also be allowable if presented in independent form.

Claims 22-31 and 42-45 depend from claim 16 either directly or indirectly, and are believed to be allowable for the same reasons as base claim 16. New claims 42-45 recite limitations found in claim 8 and specific features of R^3 found in base claim 16, and no new matter is introduced.

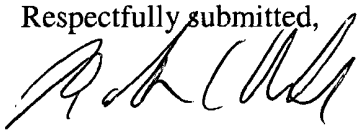
FEES

No fees should be due. Although four new claims are added, including an independent claim, in the last Office Action five claims were canceled, and the case contains less than three independent claims. However, in the event it is determined that a fee is due, please charge same to Deposit Account No. 18-1700.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-354-7540.

Respectfully submitted,



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